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| 10/789,082 | 02/27/2004 | Ugo Raffaello Citernesi | 1029.1015 | 7535 |

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MUSERLIAN, LUCAS AND MERCANTI, LLP
475 PARK AVENUE SOUTH
15TH FLOOR
NEW YORK, NY 10016

| EXAMINER | |
|---|---|
| FORD, ALLISON M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1651 | |

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/789,082 | CITERNESI, UGO RAFFAELLO | |
| | Examiner | Art Unit | |
| | Allison M Ford | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-10* is/are rejected.

7)☒ Claim(s) *1 and 2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application*

Claims 1-10 are pending in the current application.

### *Priority*

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

### *Drawings*

The drawing of Fig 2 is objected to because it does not appear to correlate to the data of Table 1 found in the specification. Table 1 in the specification shows the percentage of nitrogen present in the receptor liquid when phospholipids were present and absent. Figure 2 does not show percentage of nitrogen; rather values are measured as PROTEIN X 10, it is not clear what this measurement is of (y-axis). Furthermore, the legend is not clear as to what is being depicted, it is not clear if "PL 3-17 HSOR NAD" is intended to indicate the enzymatic pool plus NAD in the presence of phospholipids, or if "3-17" stands for something different; similarly it is not clear if "3-17 HSOR NAD" is intended to indicate the absence of phospholipids. This confusion with the legend, per se, could be remedied by simply using the labels "With Phospholipids" and "Without Phospholipids." Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings

for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

### *Claim Objections*

Claim 1 is objected to because of the following informalities: it would be more appropriate to claim, "A composition for topical use in the cosmetic or pharmaceutical field, comprising: (a) ..." It is not necessary to use both open language phrases "characterized" and "comprises." Appropriate correction is required.

Claim 2 is objected to because the name of the enzymes should read, "3-β-hydroxysteroid-oxidoreductase" and "17-α-hydroxysteroid-oxidoreductase." Also, though it is acknowledged that the terms are equivalent, applicant should remain with a single name throughout the specification and claims in reference to the enzymes; for example, on Pg. 2 of the specification the enzymes are called 3-β-hydroxysteroido-dehydrogenase and 17-α-hydroxysteroido-dehydrogenase, while on Pg. 3 of the specification and in the claims they are referred to as 3-β-hydroxysteroido-oxido-reductase and 17-α-hydroxysteroido-oxido-reductase.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The term, "comprising" as used in the composition claim 1, is a form of open language that allows for additional, non-essential elements to be included in the composition without specifically being claimed. See MPEP § 2111.03. Thus any non-essential ingredients, such as auxiliaries, additives, drugs or active principles that do not contribute additive effects to the claimed composition are included in claim 1 and should not be claimed separately. However, if the auxiliaries, additives, drugs, or active principles do have an effect or active role in the composition, they do need to be claimed, and their specific actions must also be adequately described in order to meet the written description requirement.

Therefore, due to lack of appropriate disclosure of even a single representative of a specific auxiliary, additive, drug, or active principle, the incredibly broad scope that each one of these genuses encompasses, and the lack of description of a single species, much less sufficient description of a representative number of species, which is required to claim the entire genus of auxiliaries, additives, drugs, or active principles, applicant fails to provide sufficient written description of the auxiliaries, additives, drugs, or active principles. Additionally, there is no disclosure of relevant, identifying characteristics, such as structure or other physical or chemical properties, or functional characteristics, of any of the auxiliaries, additives, drugs or active principles sufficient to show the applicant was in possession of the claimed genus. *See Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406. See MPEP § 2163.

Claims 5-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claim 5 is directed to a method of treating alopecia in mammals comprising topically applying an effective amount of a composition comprising an enzymatic pool; a coenzyme; and a vasodilator complexed with phospholipids in solution to a mammal in need of such treatment. Claim 6 requires the mammal be a human. Claim 7 requires the human to be male. Claim 8 requires the composition to be applied to the scalp of the human.

Applicant's claim 9 is directed to a method of treating alopecia in mammals comprising administering an effective amount of a composition comprising 3-β-hydroxysteroido-oxido-reductase and 17-α-hydroxysteroido-oxido-reductase, the coenzyme nicotinamido-adenin-dinucleotide (NAD) and a nicotinate derivative, as a vasodilator.

Though applicant has provided no definition for "treatment of alopecia," one of ordinary skill in the art can infer that treatment of alopecia comprises slowing or stopping the loss of hair and, optimally, regrowing hair.

It is well known that androgenic alopecia is in a large part due to the conversion of testosterone to dihydrotestosterone (DHT) by 5-α-reductase and the subsequent binding of DHT to androgen receptors that promotes expression of the genes that ultimately cause the alopecia. Therefore an inhibitor of 5-α-reductase and/or an antiandrogen that would destroy the DHT are highly sought after to prevent or reverse alopecia (See, e.g., WO 01/66702 Pg. 2, ln 1-2; US Patent 6,110,906 col. 3, ln 58-64; US Patent 4,684,635 col. 1, ln 35-41; and US Patent 5,422,371 col. 3, ln 3-5).

It appears applicant intends to claim the 3-β-hydroxysteroido-oxido-reductase and the 17-α-hydroxysteroido-oxido-reductase act as antiandrogens to change testosterone into 4-androsterone-3,17-dione, instead of dihydrotestosterone (See Spec, Pg. 2). However, applicant does not provide any evidence of this antiandrogenous action. Rather, applicant teaches a composition comprising 3-β-

hydroxysteroido-oxido-reductase, 17-α-hydroxysteroido-oxido-reductase, and nicotinamido-adenin-dinucleotide (NAD) complexed in liposomes formed by phospholipids, they did not include a vasodilator such as thurfyl nicotinate in their embodied composition (See Specification, Pg. 5). Applicant applies this composition to a skin sample *in vitro* and tests for dehydrogenase activity in the portion of the composition that successfully passes through the skin layer, thereby indicating successful infiltration through skin when applied topically (See Specification, Pg. 6-8).

It appears applicant is correlating the dehydrogenase activity in the used enzyme portion (from the receptor liquid) to an antiandrogenous effect of the composition, which would which could then be considered as a treatment for alopecia, according to the understanding in the art. However, according to Figure 3 (as there is no numerical data provided) the dehydrogenase activity was reportedly higher in the control (A), where no enzymes or coenzymes were added, compared to experimental group (D) where DHT, enzymes and the coenzyme NAD+ were added; therefore, the application of the claimed composition actually inhibited dehydrogenase activity, which applicant correlates to treating alopecia. Thus while they have showed that the enzymes can successfully pass through the skin membrane, they have failed to provide any experimental evidence that shows the enzymes successfully inhibiting the change of testosterone to dihydrotestosterone.

In fact, Labrie et al teach that 3-β-hydroxysteroid dehydrogenase actually acts similarly to 5-α-reductase in catalyzing the production of natural androgens; they target it as an enzyme to be inhibited to prevent the formation of DHT and treat alopecia (See US Patent 6,110,906 col. 6, ln 9-14); similarly, Chen et al et al teach 3-β-hydroxysteroid dehydrogenase to be an enzyme involved in the biosynthesis of androgens (See Chen et al, *J Invest Dermatol,*2002). Applicant has provided no evidence that the 3-β-hydroxysteroid dehydrogenase, by itself or in combination with the 17-α-hydroxysteroid dehydrogenase, has any effect different from that described by Labrie et al. No evidence was found in the prior art of 17-α-hydroxysteroid dehydrogenase having any antiandrogen activity; therefore without proper compelling

evidence in the current application, there is not sufficient enablement for 17-α-hydroxysteroid dehydrogenase to alter the effect of the 3-β-hydroxysteroid dehydrogenase to treat alopecia.

Therefore, due to the complete lack of experimentation and evidence of the effects of the claimed compositions on hair growth in the current application, the vast amount of experiments and work found unsuccessful on treating alopecia in the past and prior art, and the teachings of Labrie et al and Chen et al that 3-β-hydroxysteroid dehydrogenase is involved in the biosynthesis of androgens, teaching against the claimed use as an antiandrogen, applicant has failed to enable one of ordinary skill in the art to use the claimed compositions of claims 1 or 2 to successfully treat alopecia in mammals, humans, or male humans.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claim 10 is directed to a method of treating light defects in skin and appendages in mammals comprising topically applying an effective amount of a composition comprising an enzymatic pool; a coenzyme; and a vasodilator complexed with phospholipids in solution to a mammal in need of such treatment.

For the reasons stated above, namely the lack of experimental evidence or guidance or teachings on the ability of the enzyme complex to specifically treat light defects in skin and appendages in mammal, rather the reliance on the single experiment showing the capability of the enzyme complex to pass through a skin membrane, the broad scope of the composition claim, as it does not require specific enzymes or coenzymes and could read on a cell, and the vast examples of unsuccessful treatments of minor skin defects, such as acne, in the prior art, it is necessary for one to present solid and substantial

evidence in order to enable one of ordinary skill in the art to use the claimed composition for the method of treating light skin defects, thus applicant has failed to enable the use of the claimed method.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-8 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 1 is directed to a composition for topical use in the cosmetic or pharmaceutical field, comprising an enzymatic pool; a coenzyme; and a vasodilator, complexed with phospholipids in solution. This composition claim is so broad that it reads on a solution containing cells, since cells clearly contain a mixture of enzymes, coenzymes and members of the broad class of vasodilators, such as cyclic AMP (See US Patent 5,514,672, col. 21, ln 49- col. 22, ln 10). It is not clear if applicant intended to claim this composition so broadly so as to include any type and combination of enzymes, including those that would be detrimental to hair growth, such as keratinase, since this composition is intended for a treatment for alopecia in claims 5-8. Additionally, it not clear if applicant intended to claim any and all coenzymes, since they specifically point in the specification that their composition does *not* contain the hydrogenated nicotinamido-adenin-dinucleotide (NAD, *not* NADH) (See Specification, Pg. 5, ln 9-12). Claims 3-8 and 10 have the broad limitations of claim 1, and thus are rejected on the same basis.

Claim 3 recites the limitation "the nicotinic acid" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim, as claim 3 is dependent on claim 1.

Applicant's claim 4 requires the composition of claim 1 to further comprise auxiliaries, additives, drugs and active principles. It is not clear what these auxiliaries, additives, drugs or active principles

consist of. It is not clear if they are non-essential or essential ingredients, if they are essential, it is not clear how they effect the composition.

Applicant's claim 5 is directed to a method of treating alopecia in mammals, comprising applying an effective amount of the composition of claim 1 topically to a mammal in the need of such treatment. It is not clear how much is considered an effective amount. It is not clear what the desired result is, as the prevention of defluxion of hair is measured on a continuum scale; therefore, because the idea of a "successful" treatment can vary, so does the measurement of "effective amount" required to obtain that "success." Additionally, the amount required to be considered effective would also depend on the concentration of the active ingredients, at least a referenced range of concentration and amount is required so as to not exceed cell vitality limits (See Specification, Pg 8).

Applicant's claim 10 is directed to a method of treating light defects in skin and appendages in mammals, comprising topically applying an effective amount of the composition of claim 1 to the affected area of a mammal in the need of such treatment. It, again, is not clear what is considered an effective amount. Additionally, it is not clear what a "light defect" is in the skin, if it is a minor defect, or if it is a defect caused by light, no meaning or definition could be found in the specification either. Additionally, the amount required to be considered effective would also depend on the concentration of the active ingredients, at least a referenced range of concentration and amount is required so as to not exceed cell vitality limits (See Specification, Pg 8). Therefore, since it is not understood what is being treated, it is not clear what the desired results are, and thus it is not clear what an effective amount would be to achieve this unknown result.

### *Claim Rejections - 35 USC § 103*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Citernesi (WO 01/66702), in view of Bazzano (US Patent 5,514,672) and Li et al (US Patent 6,773,776).

Citernesi et al teach a composition comprising the enzyme 3-α-hydroxysteroid oxidoreductase and the coenzyme NADP(H)/NAD(H) (See Pg. 2, ln 9-24 & Claims 1-5).

Though Citernesi does not teach including a vasodilator or complexing the composition with phospholipids he does teach that the composition can further comprise other compounds that favor penetration into the lower layers of the skin of the scalp (See Pg. 3, ln 7-8). Therefore it would have been obvious to one of ordinary skill in the art to include compounds such as vasodilators and vitamins or other auxiliaries, additives, drugs or active principles and to complex the compounds in liposomes formed by phospholipids in order to promote penetration into the lower layers of the skin of the scalp as suggested by Citernesi. One of ordinary skill in the art would have been motivated to include vasodilators because Bazzano teaches vasodilators, such as thurfyl nicotinate, aid in hair growth and hair follicle stimulation by increasing the blood supply to the microvasculature around the hair follicle, thereby allowing more nutrients to enter the cells and more waste products to be carried away (See Bazzano col. 21, ln 39-53). Similarly, one would have been motivated to include such additives and auxiliaries such as vitamin $D_3$ because it has been shown to regulate and promote cell differentiation of keratinocytes; additionally, it has been shown to assist in the conversion of vellus to terminal hairs (See Bazzano col. 21, ln 25-38). One would have expected success using vasodilators such as thrufyl nicotinate and additives and auxiliaries such as vitamin $D_3$ because Bazzano teaches using vasodilators and vitamin $D_3$ in a similar process of treating alopecia with no adverse consequences from the thurfyl nicotinate or vitamins. Additionally, one of ordinary skill in the art would have been motivated to complex the enzymes, coenzymes, vasodilators, and any additives or auxiliaries in a liposome made of phospholipids because Li et al teach liposomes, well known in the art to be comprised of phospholipids, can selectively target the hair follicles and be used to enhance delivery of compounds complexed in the liposome across the stratum

corneum to deliver the compounds to the hair follicle (See Li et al col. 3, ln 19-21). One would have expected success because Li et al demonstrate success using liposomes, comprised of phospholipids, to deliver compounds directly to hair follicles for the purpose of alopecia treatment.

Though Citernesi only teaches use of the single enzyme 3-α-hydroxysteroid oxidoreductase, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include additional enzymes with similar effects to create an "enzymatic pool" with enhanced effect. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Citernesi teach the composition can be used to treat alopecia by applying topically to the scalps of male humans (See Pg. 7, ln 17-19 & Pg 8, ln 12-15). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Citernesi to include the aforementioned additional similar acting enzymes, vasodilators and additional additives or auxiliaries, all complexed in a phospholipid liposome in order to increase penetration into the hair follicles and to enhance growth of the cells being treated. One would have been motivated to apply the modified composition in order to increase chances of successful treatment of the alopecia, and would have expected success because each of the additional modifications enhances the original composition, as taught above. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M Ford whose telephone number is 571-272-2936. The examiner can normally be reached on M-F 7:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651